REMARKS

Reconsideration and withdrawal of any rejections of the application, and allowance of the claims, especially in view of the remarks made herein, and the accompanying Declaration (incorporated herein by reference), are respectfully requested.

Claims 1-17, are pending in this application and claims 7, 8, 10, 13 and 16 are now amended. It is submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§101, 102, 103 and 112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the addition and amendments to the claims are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the new claims is found throughout the specification and from the originally-filed claims; no new matter is added.

In addition, submitted herewith is the original signed declaration of Dr. Edward Maytin (Tab A). But, it is noted that 37 C.F.R. § 1.4(d)(1)(ii) allows for "a copy" not bearing an "original signature" to be acceptable as an original. Reconsideration and withdraw of the objection to the inventor's Declaration are respectfully requested.

The typos noted by the Examiner are corrected and the Examiner is thanked for carefully reading the application. Further, it is believed that trademarks are used correctly; for instance, at page 1, the trademark is used with initial capitalization, a TM symbol, and a description. The Examiner is invited to clarify that which is sought at page 2 of the Office Action, and/or reconsider and withdraw the objection to the specification.

THE REJECTION UNDER 35 U.S.C. § 112 IS OVERCOME

The Application Provides an Enabling Disclosure and the Claims are Definite

Claims 1-13 and 17 are rejected to under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of detecting unwanted cellular proliferation using photodynamic therapy in combination with a differentiation factor in an *in vitro* culture system, allegedly does not reasonably provide enablement for treating a subject of unwanted cellular proliferation using said method *in vivo*. Claims 7, 10, 13, and 16 are further rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claims 14 and 15 are not rejected under 35 U.S.C. § 112, first or second paragraph. It is respectfully submitted that the pending claims are definite, and the present application does enable one skilled in the art to make and use the claimed invention.

The present invention relates to methods for the integration of photodynamic therapy (PDT) and differentiation therapy (DT) in the inhibition and analysis of unwanted cellular proliferation. The inventive methods comprise inducing differentiation in a proliferating cell (DT) and providing photosensitizer to the cell followed by irradiation and photoactivation of the photosensitizer within the cell (PDT). Integration of PDT with DT enhances the inhibition of unwanted cellular proliferation.

Submitted herewith is the Declaration of Dr. Bernhard Ortel, an inventor of the present application as well as one of skill in the art (Tab B). The Declaration provides a thorough review of the claimed methods, embraced by those of skill in the art, for treating disorders characterized by cellular proliferation. In addition, Dr. Ortel presents further data, consistent with the teaching in the specification, demonstrating successful reduction of tumor growth *in vivo* following a normal course of combination DT/PDT treatment. As discussed in the Declaration, the claimed methods can be carried out by one skilled in the art without undue experimentation.

The clinical use of photosensitizers is well known in the art. To date, several thousand patients have been treated with PDT for a variety of neoplasms. Randomized clinical trials of this modality using Photofrin® were initiated as early as 1987. These first randomized trials were sponsored by Quadra Logic Technologies, Inc. (now QLT Phototherapeutics, Vancouver,

Canada) and American Cyanamid Co. (Pearl River, New York), and compared the efficacy of PDT with that of other forms of therapy for bladder, esophageal, and lung cancers. Within the past 5 years, significant progress has been made worldwide in obtaining regulatory approval for a variety of indications. Currently, PDT with the photosensitizer Photofrin® is approved in at least 10 countries. Approval for treatment with other photosensitizers has been requested in the United States, Canada, and Europe.

It is well known in the art that PDT is a binary therapy, having the advantage of inherent dual selectivity. First, an increased concentration of photosensitizer accumulates in target tissues. (Photosensitizers preferentially accumulate within proliferating cells, such as those comprising neoplastic tissues). Second, the irradiation can be specifically delivered to the target tissue in a controlled volume. Photoactivation will be limited to only those irradiated areas that have accumulated sufficient amounts of photosensitizer. Thus, even if the photosensitizer does bind to normal tissue, the tissue will either not be targeted for irradiation or not contain the threshold level of photosensitizer necessary for photoactivation.

Selectivity can be even further enhanced by attaching photosensitizers to molecular delivery systems that have high affinity for the proliferating cells of interest. For example, the specification teaches that one way to improve selectivity is to link the photosensitizer to a targeting moiety. See the specification, page 3, lines 20-22; page 14, lines 1-19. The targeting moiety delivers the photosensitizer directly to the proliferating cells of interest.

The clinical use of differentiation factors is also well known in the art. As discussed in the specification, the retinoids have long been used in the clinical treatment of acute promyelocytic leukemia. See the specification, page 18, lines 20-24. Clinical use of differentiation therapy in the treatment of cancer and diabetes is well within the skill of one in the art. See the specification, page 18, lines 20-31; page 19, lines 1-11. Thus, the differentiation factor selected can be any known in the art to cause differentiation of the proliferating cell type (e.g. retinoids for use with DT of hematopoietic disorders).

The specification teaches methods of administering the differentiation factor (page 6, lines 8-12; page 8, lines 3-11) and the photosensitizer (page 8, lines 3-11; page 13, lines 12-19), including the timing and sequence of administration (page 6, lines 8-12; page 7, lines 8-17). The

specification further teaches methods of photoactivation (page 13, lines 21-29). Methods for administering photosensitizer compositions and carrying out photoactivation are known in the art, and are described, for example, in U.S. Patent No.s 5,952,329, 5,807,881, 5,798,349, 5,776,966, 5,789,433, 5,736,563, and 5,484,803 (Tab C). PDT depends on various factors, including the amount of the photosensitizer administered, the wavelength of the photoactivating light, the intensity of the photoactivating light, and the duration of illumination by the photoactivating light. Thus, PDT can be adjusted to a therapeutically effective level by adjusting one or more of these factors, either alone or in combination with DT as described in the specification (page 6, lines 8-12; page 7, lines 8-17; page 8, lines 3-11). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub. nom.; *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). The adjustments above are routine and within the ordinary skill in the art. Accordingly, practicing the invention as claimed requires no undue experimentation.

The specification provides six working examples. See the specification, page 20, lines 16-27; page 21. Examples 1-3 show reduced survival of human prostate cancer cells following combination PDT/DT treatment *in vitro*. Examples 5 and 6 show increased accumulation of the photosensitizer PpIX in cancer cells following pretreatment with DT *in vitro* and *in vivo*, respectively. The declaration of Dr. Ortel, which is consistent with the teaching in the specification, shows a reduction of tumor weight *in vivo* following combination PDT/DT treatment. The weight of the evidence before the Office is more than sufficient to demonstrate the specificity and potency of the inventive methods.

MPEP 2164.02(c) provides guidelines to follow in determining whether a showing of success by an applicant using *in vitro* data supports claims directed to the analogous *in vivo* application. An *in vitro* model is acceptable where it is recognized in the art that this model correlates to a specific *in vivo* condition. If this is has not yet been established in the art, the *in vitro* model is acceptable if one skilled in the art would accept the model as *reasonably*

correlating to the condition. The "reasonableness" standard serves to prevent the PTO from unnecessarily and inappropriately adopting the more stringent standards of the FDA.[1]

In the present invention, the "condition" of MPEP 2164.02(c) is any condition characterized by unwanted cellular proliferation in a subject. The "condition" can be alleviated by inhibition of the unwanted cellular proliferation. When testing a therapy for inhibition of unwanted cellular proliferation, a good experimental model should test whether 1) the therapy will target the cells of interest and whether 2) the proliferation is inhibited as a result. If this test is carried out in *in vitro* and it is successful, the result is reasonably predictive of success *in vivo*. For the inventive methods, results *in vitro* have been shown to correlate with results *in vivo*.

The Declaration of Dr. Ortel and the teaching in the specification show that DT/PDT will successfully inhibit unwanted proliferation in neoplastic tissues *in vitro* and *in vivo*. Further, DT/PDT can be carried out with specificity as well as potency. As discussed above and in the declaration, there are at least three levels of selection contributing to the specificity of the inventive methods:

- The differentiation factor will selectively target proliferating cells
- The photosensitizer will selectively target proliferating cells and as a result, the proliferating cells accumulate substantially greater amounts of photosensitizer
- The activating light can be targeted directly to the proliferating cells, and delivered in amounts specific to the level of photosensitizer that has accumulated only in those cells

Thus, the inventive methods can be practiced with specificity and potency by one of skill in the art and without the need for undue experimentation.

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[1] Public hearings were held in San Diego on October 17, 1994, where then PTO Commissioner Bruce Lehman and other PTO representatives received comments on the inappropriate standards that Examiners were applying to biotechnological inventions and as a result of these and other objections raised by the scientific community, the present "reasonableness" standard is now applied.

The applicants should not be required to provide further experimental data in order for the full scope of the claims to be allowed. Given the strong showing of success both *in vitro* and *in vivo* with the inventive methods, and the positive correlation between *in vitro* and *in vivo* results, the full scope of the claims, as amended, is allowable. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985) ("based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence); *see also In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Further experimentation, such as in human subjects, is clearly not required. The PTO is not the FDA.

The applicants have shown that the inventive methods are specific, potent and effective *in vivo*. All of the Examiner's concerns have been addressed herein and in the accompanying Declaration of Dr. Ortel. Reconsideration and withdraw of the rejections under 35 U.S.C. § 112 is respectfully requested.

THE REJECTION UNDER 35 U.S.C. § 102 IS OVERCOME

Momma Does Not Disclose Every Element of Claims 14-15

Claims 14-15 are rejected under 35 U.S.C. § 102, as being anticipated Momma et al ("Momma"). Momma discloses the effect of 5α-dihydrotestosterone (DHT) on the accumulation of PpIX in hormone responsive LNCaP cell lines *in vitro*. Momma does not disclose the use of DT/PDT for use in detecting a cell characterized as having unwanted proliferation in a subject. Reconsideration and withdraw of the rejections under 35 U.S.C. § 102 is respectfully requested.

A 35 U.S.C. § 102 rejection must show that each and every element of the claimed invention is found in a single reference. Momma fails to fulfill this criterion. Claims 14-15 require at least two elements not disclosed by Momma:

- providing a differentiation agent to a cell of a subject

- detecting the difference between the cell and a control cell, thereby detecting the presence of a disorder characterized by unwanted cell proliferation

Momma discloses the use of DHT on LNCaP cell lines *in vitro*. As shown by Momma in Table 1, and as discussed throughout the reference, DHT stimulates proliferation in LNCaP cell lines. DHT does not promote differentiation of LNCaP cell lines. According to Momma, "most primary prostate cancers are androgen-dependent" and require growth factors such as DHT to stimulate growth. See Momma, page 1062, first column, last sentence; page 1065, second column, stating "It has been found that there is an optimum added DHT concentration for maximum stimulation of proliferation of LNCaP cells." DHT, as used by Momma, is not a differentiation factor but a growth stimulating factor. Thus, Momma fails to "provide a differentiation agent" as in claims 14-15.

Momma studies the effect of hormonal modulation on the accumulation of PpIX, so that the effects of PpIX-based PDT on hormonally regulated prostate cancers can be better understood. Momma does not disclose a method for detecting a disorder characterized by unwanted cell proliferation. Momma discloses only the increase in PpIX levels within DHT-treated LNCaP cells and does not disclose the use of this combination, or any combination, for diagnostic purposes.

Momma does not disclose every element of claims 14-15 and therefore cannot be cited against these claims under 35 U.S.C. § 102. Reconsideration and withdraw of the rejections under 35 U.S.C. § 102 is respectfully requested.

THE REJECTION UNDER 35 U.S.C. § 103 IS OVERCOME

The Cited References Do Not Teach or Suggest the Inventive Methods

Claims 1-13, and 16-17 are rejected under 35 U.S.C. § 103, as being unpatentable over Momma, in view of Skalkos et al ("Skalkos"). Momma does not suggest the use of a differentiation factor, much less DT/PDT, for the treatment unwanted cellular proliferation in a

subject. Skalkos does not suggest the use of a differentiation factor together with PDT for the treatment unwanted cellular proliferation in a subject and therefore fails to cure the defects of Momma. Reconsideration and withdraw of the rejections under 35 U.S.C. § 103 is respectfully requested.

Momma shows that the effect of DHT on LNCaP cell lines *in vitro* is to stimulate proliferation and cause accumulation of PpIX. Momma discourages the use of DHT *in vivo* by acknowledging that the proliferative effect of DHT is undesirable:

> If it could be established precisely what the mechanism of DHT enhanced PpIX accumulation was, then it might be possible to design a molecule that would increase PpIX accumulation without having a growth stimulatory effect. See Momma, page 1066, second column, third paragraph.

Momma suggests the need for a molecule that will "increase PpIX accumulation without having a growth stimulatory effect" *in vivo*. Momma makes clear that DHT is not a viable candidate. However, Momma does not suggest that a differentiation factor would satisfy this need. If anything, Momma teaches away from the use of a differentiation factor by showing that the accumulation of PpIX is associated with the use of a growth stimulating factor (which has the opposite effect). Thus, Momma does not disclose the inventive methods or suggest the need therefor.

Skalkos also fails to suggest the use of a differentiation factor in combination with PDT. In this regard, Skalkos suffers from the same shortcoming as Momma. Taken alone or in combination, the cited references fail to teach or suggest the inventive methods. Reconsideration and withdraw of the rejections under 35 U.S.C. § 103 is respectfully requested.

Moreover, in view of the amendment, remarks, attachments and Declaration herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

If any issue remains as an impediment to allowance, a further interview with the Examiner and the Examiner's SPE, Dr. Anthony Caputa[2], are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

Respectfully submitted,
Attorneys For Applicants
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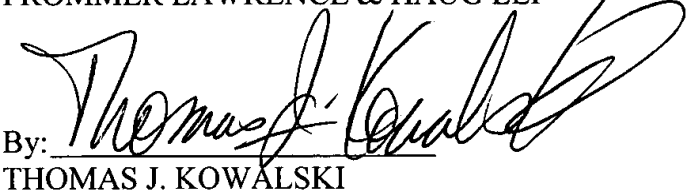
By: 
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[2] The undersigned would appreciate the review and presence of SPE Caputa, as the undersigned has had the pleasure of working with SPE Caputa in other, unrelated, applications.

APPENDIX 1: MARKED-UP VERSION OF AMENDMENTS

IN THE CLAIMS:

7. (Amended) The method of claim 1, [wherein] further comprising administration to the subject of a compound which causes the accumulation of a PS, the formation of a PS, or is converted to a PS, in the subject's body [is administered to the subject].

8. (Amended) The method of claim [7] 1, [wherein] further comprising administration to the subject of a compound which causes the accumulation of, the formation of, or which is converted to a porphyrin, in the subject's body [is administered to the subject].

10. (Amended) The method of claim 1, wherein the subject has a [hematopoietic disorder,] and a PS and a retinoic acid, are administered to the subject.

13. (Amended) The method of claim 1, wherein [a tumor cell] a proliferating cell is induced to differentiate and the PS is supplied such that it is present while the cells are in a state of induced differentiation.

16. (Amended) The method of claim [14] 15, wherein the photosensitizer includes chlorin e6 or a chlorin derivative.

IN THE SPECIFICATION:

Specification, at page 19, fourth and fifth paragraphs:

--[Flouresence] Fluorescence photodetection of cancers involves the excitation of a chromophore with light and monitoring the emitted light as fluorescence. The combination of treating a cell in a subject suspected of having a neoplasia with a differentiating agent, and a light emitting agent, e.g., a photosensitizer or a fluorescent compound, allows for a marked increase in light emission upon differentiation of the cell, e.g., both for endogenous [(autoflourescence)] (autofluorescence) and exogenous fluorescence (induced fluorescence). This method can be performed in vivo, or a sample can be taken from a subject and [preformed] performed ex vivo.

The enhancement of contrast afforded by this method is useful for the *in vivo* detection of early neoplasias. Moreover, the improved contrast also provides a method of enhancing the delineation of margins of resection. For example, the present method can be used to determine

the effectiveness of tumor treatment. For example, following tumor treatment, the [efficiacy] efficacy of the treatment can be determined by using the method to determine any residual or new tumor growth, and if necessary the tumor can be retreated.